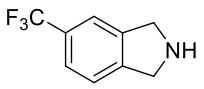
Summary

It has now been found that the compound of formula (1A) or a pharmaceutically acceptable salt thereof can be prepared using a process and a synthesis route, which is more practical, economical and suitable for use in a large scale. Intermediate compounds are prepared with improved methods utilizing commercially available starting materials and resulting in acceptable yields. Moreover, the compound of formula (1A) is obtained as a high purity and low colored product directly by crystallization without the need of purification by chromatography.

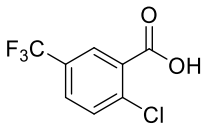
Thus, the present disclosure provides a process for the preparation of a compound of formula (V) or a pharmaceutically acceptable salt thereof



(V)

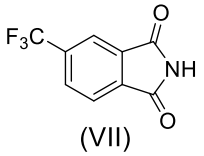
comprising the steps of either

a) treating a compound of formula (VI)



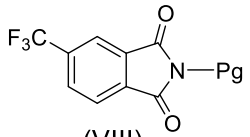
(VI)

with copper cyanide to obtain a compound of formula (VII)



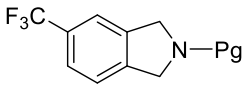
(VII) ;

b) protecting the compound of formula (VII) to obtain a compound of formula (VIII) wherein Pg is a protecting group



(VIII) ;

c) reducing the compound of formula (VIII) to obtain a compound of formula (IX)

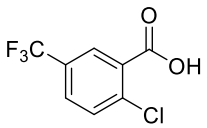


(IX) ; and

d) deprotecting the compound of formula (IX) to obtain a compound of formula (V); and optionally converting it to its pharmaceutically acceptable salt;

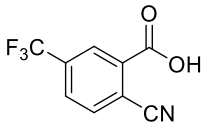
or

a') treating a compound of formula (VI)



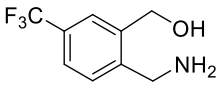
(VI)

with hexacyanoferrate[II] salt in the presence of a catalyst to obtain a compound of formula (X) or a pharmaceutically acceptable salt thereof



(X) ;

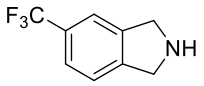
b') reducing the compound of formula (X) or a pharmaceutically acceptable salt thereof to obtain a compound of formula (XI) or a pharmaceutically acceptable salt thereof



(XI) ;

c') treating the compound of formula (XI) or a pharmaceutically acceptable salt thereof with thionyl chloride to obtain a compound of formula (V); and optionally converting it to its pharmaceutically acceptable salt.

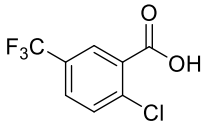
In one aspect, the present disclosure provides a process for the preparation of a compound of formula (V) or a pharmaceutically acceptable salt thereof



(V)

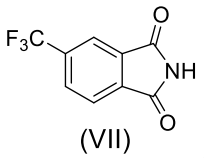
comprising the steps of

a) treating a compound of formula (VI)



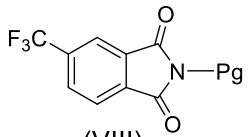
(VI)

with copper cyanide to obtain a compound of formula (VII)



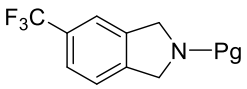
(VII) ;

b) protecting the compound of formula (VII) to obtain a compound of formula (VIII) wherein Pg is a protecting group



(VIII) ;

c) reducing the compound of formula (VIII) to obtain a compound of formula (IX)

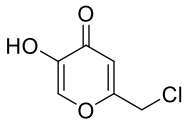


(IX) ; and

d) deprotecting the compound of formula (IX) to obtain a compound of formula (V); and optionally converting it to its pharmaceutically acceptable salt.

In another aspect, the present disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof

a'') reacting a compound of formula (XII)



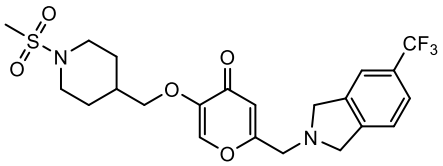
(XII)

with hydrochloride salt of 5-(trifluoromethyl)isoindoline (V) in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b'') adding isopropyl alcohol and water to the mixture; and

c'') isolating the compound of formula (III).

In still another aspect, the present disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof

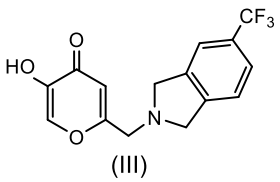


(1A)

comprising the steps of

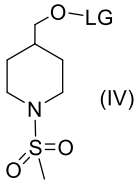
i') preparing a compound of formula (III) according to any of the processes as defined above;

ii') reacting the compound of formula (III)



(III)

with a compound of formula (IV)

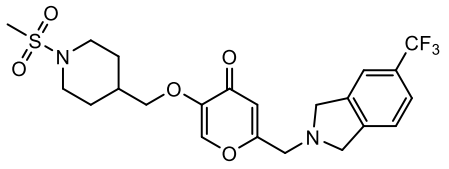


(IV)

wherein LG is a leaving group selected from a mesyl or a tosyl group,

to produce compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

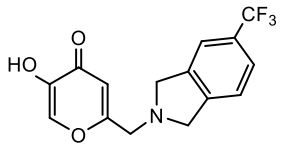
In still another aspect, the present disclosure provides a process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

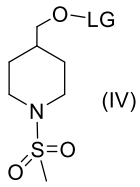
comprising the steps of

i'') reacting a compound of formula (III)



(III)

with a compound of formula (IV);



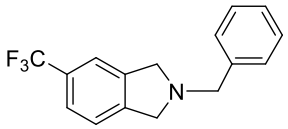
(IV)

in dimethyl sulfoxide in the presence of cesium carbonate, wherein LG is a leaving group selected from a mesyl or a tosyl group;

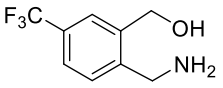
ii'') adding acetonitrile and water to the mixture; and

iii'') isolating the compound of formula (1A); and optionally converting it to its pharmaceutically acceptable salt.

The present disclosure provides new intermediate compound of formula (IXa), or (XI) or a pharmaceutically acceptable salt thereof



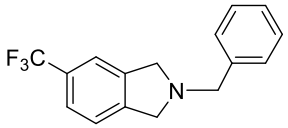
(IXa)



(XI)

.

In another aspect, the present disclosure provides new intermediate compound of formula (IXa), or a pharmaceutically acceptable salt thereof



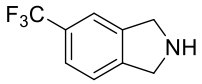
(IXa)

.

Detailed description of the invention

Claims

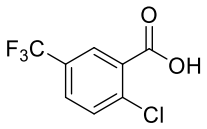
1. A process for the preparation of a compound of formula (V) or a pharmaceutically acceptable salt thereof



(V)

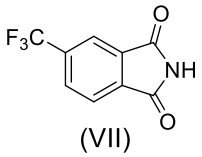
comprising the steps of

a) treating a compound of formula (VI)



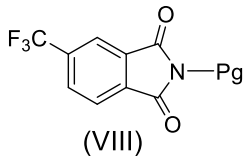
(VI)

with copper cyanide to obtain a compound of formula (VII)



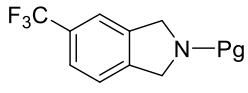
(VII) ;

b) protecting the compound of formula (VII) to obtain a compound of formula (VIII) wherein Pg is a protecting group



(VIII) ;

c) reducing the compound of formula (VIII) to obtain a compound of formula (IX)



(IX) ; and

d) deprotecting the compound of formula (IX) to obtain a compound of formula (V); and optionally converting it to its pharmaceutically acceptable salt.

2. The process according to claim 1, wherein step a) is carried out in dimethylacetamide.

3. The process according to any of the preceding claims, wherein the reaction temperature at step a) is from about 100 to about 140 °C, preferably from about 120 to about 135 °C.

4. The process according to any of the preceding claims, wherein the reaction of step a) is followed by addition of ferric chloride in water and aqueous hydrochloric acid.

5. The process according to any of the preceding claims, wherein Pg is a benzyl group.

6. The process according to claim 5, wherein step b) comprises reacting compound of formula (VII) with benzyl bromide in the presence of a base.

7. The process according to claim 6, wherein the base is potassium carbonate.

8. The process according to any of the preceding claims, wherein step b) is carried out in dimethylacetamide.

9. The process according to any of the preceding claims, wherein step c) comprises treating the compound of formula (VIII) with borohydride salt and boron trifluoride tetrahydrofuran complex.

10. The process according to claim 9, wherein the borohydride salt is sodium borohydride.

11. The process according to any of the preceding claims, wherein step c) is carried out in tetrahydrofuran.

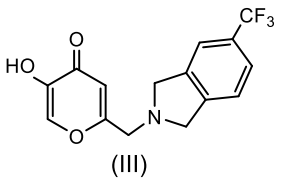
12. The process according to any of the preceding claims, wherein step d) comprises hydrogenation in the presence of a catalyst.

13. The process according to claim 12, wherein the catalyst is a palladium catalyst.

14. The process according to any of the preceding claims, wherein step d) is carried out in methanol.

15. The process according to any of the preceding claims, wherein after step d) the obtained compound of formula (V) is converted to its hydrochloride salt.

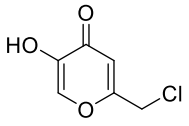
16. A process for the preparation of a compound of formula (III)



(III)

comprising the steps of

a'') reacting a compound of formula (XII)



(XII)

with hydrochloride salt of 5-(trifluoromethyl)isoindoline (V) in dimethyl sulfoxide in the presence of N,N-diisopropylethylamine;

b'') adding isopropyl alcohol and water to the mixture; and

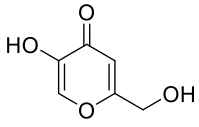
c'') isolating the compound of formula (III).

17. The process according to claim 16, wherein step b'') further comprises addition of acetic acid.

18. The process according to claim 16 or 17, wherein before step c'') the mixture is cooled to a temperature which is form about 5°C to about 15 °C.

19. The process according to any one of claims 16 to 18, wherein hydrochloride salt of 5-(trifluoromethyl)isoindoline (V) is prepared according to any one of claims 1 to 15.

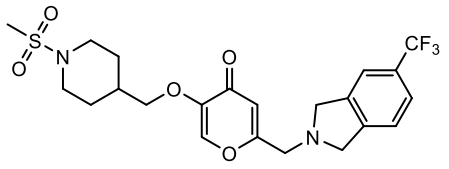
20. The process according to any one of claims 16 to 19, wherein the compound of formula (XII) is prepared by reacting a compound of formula (XIII)



(XIII)

with thionyl chloride in acetonitrile, adding water, and isolating the compound of formula (XII).

21. The process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof

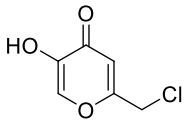


(1A)

comprising the steps of

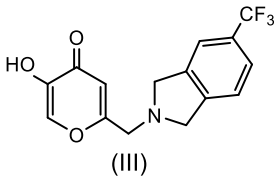
i) preparing hydrochloride salt of 5-(trifluoromethyl)isoindoline (V) according to the process of any one of claims 1 to 15;

ii) reacting hydrochloride salt of 5-(trifluoromethyl)isoindoline (V) with a compound of formula (XII)



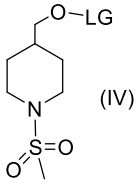
(XII)

to produce a compound of formula (III);



(III)

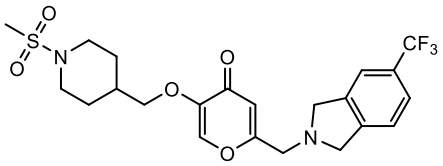
iii) reacting a compound of formula (III) with a compound of formula (IV)



(IV)

wherein LG is a leaving group selected from a mesyl or a tosyl group, to produce compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

22. A process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof

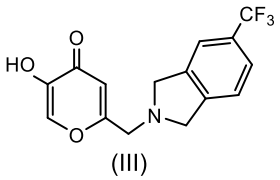


(1A)

comprising the steps of

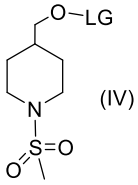
i') preparing a compound of formula (III) according to the process of any one of claims 16 to 20;

ii') reacting the compound of formula (III)



(III)

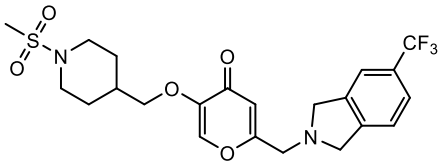
with a compound of formula (IV)



(IV)

wherein LG is a leaving group selected from a mesyl or a tosyl group,
to produce compound of formula (1A), and optionally converting it to its pharmaceutically acceptable salt.

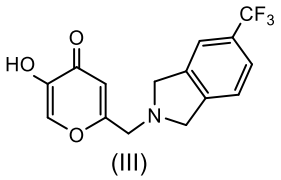
23. A process for the preparation of a compound of formula (1A) or a pharmaceutically acceptable salt thereof



(1A)

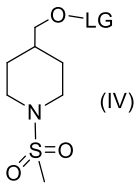
comprising the steps of

i'') reacting a compound of formula (III)



(III)

with a compound of formula (IV);



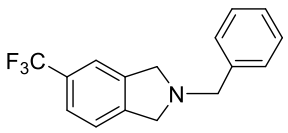
(IV)

in dimethyl sulfoxide in the presence of cesium carbonate, wherein LG is a leaving group selected from a mesyl or a tosyl group;

ii'') adding acetonitrile and water to the mixture; and

iii'') isolating the compound of formula (1A); and optionally converting it to its pharmaceutically acceptable salt.

24. New intermediate compound of formula (IXa), or a pharmaceutically acceptable salt thereof



(IXa) .